patient's antigen-specific T cells respond is transferred into the APCs. The APCs are reintroduced into the patient and activate the auto-antigen specific T cells. A product is administered to the patient that is detrimental to activated T cell proliferation. (Claim 41.)

The invention is also drawn to APCs of an autoimmune disease patient that are transduced or transfected with a polynucleotide. The polynucleotide encodes a protein comprising all or a portion of an auto-antigen to which the patient's antigen-specific T cells respond. The auto-antigen or portion of the auto-antigen is functionally connected to a signal peptide and a transmembrane/cytoplasmic tail. The auto-antigen or portion of the auto-antigen is processed by endosomes as a result of these functional connections. (Claim 54.)

The invention is also drawn to a virus that infects human APCs. The virus comprises a polynucleotide that encodes all or a portion of an auto-antigen to which the autoimmune disease patient's antigen-specific T cells respond. (Claim 58.)

The Rejection of Claims 41-67 Under 35 U.S.C. § 112

Claims 41-67 are rejected under 35 U.S.C. § 112 for lack of enablement. Applicant respectfully traverses.

In order to satisfy the enablement requirement the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The Patent Office has asserted two reasons for the enablement rejection in the Advisory Action. First, the claims are rejected because the specification fails to disclose experimental data corresponding to the invention as claimed. The Advisory Action alleges that "in unpredictable fields,

when the prior art, in this case ex vivo gene therapy is not enabled across the board, the onus is on the applicants to support that which is claimed by analogous experimentation." (Paper 17, page 2, lines 9-11.) The accompanying Declaration under Rule 132 provides the "analogous experimentation" requested by the Patent Office and demonstrates that one of skill in the art could make and use the claimed invention without undue experimentation.

Second, the Advisory Action asserts that the method claims recite that T cells are modified to contain a nucleotide sequence encoding an auto-antigen and a detrimental product to T cells, such as FasL. Thus it is possible that the modified T cells will be ablated before they are administered to the patient.

> [T]he instant invention is directed to a method of ablating T cells which had been modified previously by a nucleotide encoding the autoantigen and when reintroduced into the individual another product such as Fas ligand of FADD is added. The narrower claims however recite that the Fas ligand or FADD is also expressed by the T cells. Therefore, it is still unclear if the product which is detrimental to the T cells will be expressed prior to administration and then the question is will the T cells be ablated even before they are administered?

Paper 17, Advisory Action at page 2, lines 4-8.

The claimed methods do not however involve modification of T cells by nucleic acids encoding auto-antigens or that T cells are modified to express Fas ligand or FADD. Rather, APCs are so modified. Independent claim 41 recites, "transferring into the APCs a polynucleotide which encodes all or a portion of an auto-antigen to which the patient's antigen-specific T cells respond." The product detrimental to T cells is also transferred into APCs. Dependent claim 46 recites, "wherein the APC cells which express FAS ligand and a truncated form of FADD are the same cells which express auto-antigen." Thus the claimed methods do not require removal and transfection of T cells. It is APCs that are removed, modified and reintroduced into the patient. Thus the T cells, which remain in the patient during the *ex vivo* steps, are not ablated outside of the body of the patient.

The claimed methods are enabled such that one of skill in the art could make and use the claimed invention without resorting to undue experimentation. Withdrawal of this rejection to method claims 41-53 and 65 is respectfully requested.

Furthermore, claims 54-64 and 66-67 drawn to antigen presenting cells and viruses are enabled. The Patent Office asserted no separate reasons why these claims fail to meet the enablement requirement in the Advisory Action. In past Office Actions, however, the Patent Office has asserted that these claims are not enabled. Each of these assertions has seemingly been based on the assumption that the APCs or the viruses must be used for gene therapy. The Patent Office has asserted that the viral vectors of independent claim 58 are not enabled because they may not be tolerated in patients. "[A]pplicants are not enabled for any virus comprising (1) AchR (AA 1-210), (2) FasL and (3) truncated FADD, which are transfected into APCs as claimed in claim 58 specifically, as the virus may retain deleterious parts which may be rejected *in vivo* applications." (Paper 15, page 7, lines 2-5.)

The MPEP § 2164.01(b) sets forth that:

> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833 (CCPA 1970).

Thus, only one method of making and using the claimed invention must be taught in the specification. As demonstrated by the accompanying declaration under Rule 132 the claims drawn to APCs and viruses are enabled for use in *ex vivo* gene therapy. However, even if, *arguendo*, the Patent Office finds that *ex vivo* therapy is not enabled, the claims to viruses and APCs would still be enabled. The specification discloses that the claimed APCs and viruses can be used to screen and identify treatments that arrest the growth of antigen-specific T cells or eliminate antigen-specific T cells in a model system. The specification discloses that "antigen-specific T cell activation provides

a model system in which drugs and treatments can be screened to identify those which are effective in arresting growth of or eliminating the antigen-specific T cells." (Page 5, lines 21-23.) The APCs may be used in such a model system. The viruses may be used to transduce these APCs used in the model system. Thus the specification supports at least one method for making and using the claimed APCs and viruses that correlates with the entire scope of these claims. Withdrawal of this rejection to claims 54-64 and 66-67 is respectfully requested.

As alluded to above, Applicant submits a Declaration Under Rule 132 to demonstrate that the disclosure is enabling. The declaration demonstrates that isolated antigen presenting cells (APCs) transduced with a recombinant viral vector containing genes encoding a specific antigen, a detrimental product and truncated FADD are effective in killing T cells that recognize the specific antigen in an animal.

The animals that were used in the experiments described in the declaration were transgenic mice that express the T cell receptor for HA. APCs were removed from the HA transgenic mice and infected with a recombinant vaccinia virus vector (VVV). One recombinant VVV was used to generate APCs specific for HA-specific T cells. This VVV was genetically engineered to contain three genes. The three genes encoded HA, FasL, and truncated FADD. A second recombinant VVV was used to produce control APCs. This recombinant VVV was genetically engineered to contain two genes. The two genes were FasL and truncated FADD.

The transduced APCs specific for HA were reintroduced into a first HA transgenic mouse. The transduced control APCs were reintroduced into a second transgenic mouse. Two additional HA transgenic mice were not injected with transduced APCs and served as untreated controls.

The first HA transgenic mouse exhibited HA-specific T cell killing. The percentage of HA-specific $CD4^+$ T cells in the total $CD4^+$ T cell population of PBLs was significantly less in the first HA transgenic mouse than in the second HA transgenic mouse or than in the untreated control mice.

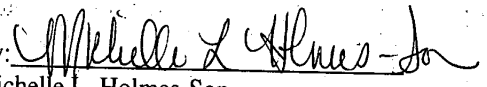
See Declaration at Paragraph 7 and Table 1. Proliferation of splenocytes and lymph node cells in response to HA was also significantly reduced in the first HA transgenic mouse compared to the second HA transgenic mouse or to the untreated control mice. See Declaration at Paragraph 9 and Table 2.

The declaration therefore demonstrates that the claimed method of (1) activating a particular antigen-specific T cell population with APC specific for that population, and (2) administering a detrimental product to the activated population in fact ablates antigen-specific T cells. The declaration demonstrates that one of skill in the art would not have to resort to undue or unreasonable experimentation to successfully practice the methods of the claimed invention. Thus the claims are enabled.

Withdrawal of the rejection to claims 41-67 is respectfully requested.

Respectfully submitted,

Date: February 13, 2002

By: 
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